Attorney Docket No: SALK3140-1 (088802-9803)

Application No: 10/535,042 Filing Date: January 9, 2006

Supplemental Response to OA (mailed 2/17/09)

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## Amendments to the Claims/Listing of Claims

Please amend claims 14, 18, 19 and 31 as follows. In addition, please cancel claims 1-3, 6-13, 15, 21-23, 32 and 33 without prejudice. This listing of claims will replace all prior versions, and listings, of claims in the application:

## 1. - 13. Cancelled

 (Currently amended) A method of screening molecules to determine those which are capable of binding to a farnesoid X receptor (FXR) molecule, said method comprising:

modeling a test molecule that potentially interacts with [[a]] the ligand binding domain of [[a]] said farnesoid X receptor (FXR) molecule, said ligand binding domain comprising amino acid residues 248 - 476 of SEQ ID NO:1,

wherein said ligand binding domain is <u>further</u> defined by a <u>plurality of the</u> structure coordinates of the <u>ligand binding domain of a FXR-molecule or a fragment</u> thereof, and

wherein said structure coordinates are based on X-ray-diffraction data obtained from crystals of said FXR molecule or molecular complex, or a homologue of said FXR molecule or molecular complex, set forth in Appendix 1, and

determining whether there is repulsive electrostatic interaction between said test molecule and said FXR molecule,

whereby those compounds test molecules which lack repulsive electrostatic interaction with <u>said</u> FXR molecule in their bound state are capable of binding to a farnesoid X receptor (FXR) molecule therefor.

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## 15. - 17. Cancelled.

- 18. (Currently amended) A method according to claim 14, wherein said test molecule is developed using a computer algorithm to predict a three-dimensional representation of said test molecule interacting with a FXR molecule based upon a three-dimensional representation of a FXR molecule or fragment thereof.
- (Currently amended) A method of screening compounds to determine those with agonist, partial agonist, or antagonist activity with respect to a farnesoid X receptor (FXR) molecule, said method comprising:
  - (a) modeling a test compound that potentially interacts with [[a]] the ligand binding domain of [[a]] said farnesoid X receptor (FXR) molecule, said ligand binding domain comprising amino acid residues 248 476 of SEQ ID NO:1,

wherein said ligand binding domain is <u>further</u> defined by <u>a plurality</u>
of <u>the</u> structure coordinates of <u>a crystalline form of the ligand binding</u>
domain of a FXR molecule or a fragment thereof, and

wherein said plurality of structure coordinates are based on X-ray diffraction data obtained from crystals of said FXR molecule or molecular complex, or a homologue of said FXR molecule or molecular complex set forth in Appendix 1; and

 (b) determining the ability of said test compound to modulate the activity of said FXR molecule in the optional presence of a known FXR agonist,

whereby those molecules test compounds which bind and alter the activity of farnesoid X receptor (FXR) molecule are identified as agonists or partial agonists, and those test compounds which bind but do not alter the activity of farnesoid X receptor (FXR) molecule are identified as antagonists therefor.

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- 20. 30. Cancelled
- (Withdrawn; currently amended) A method for determining whether a test compound is capable of binding to the ligand binding domain of a farnesoid X receptor (FXR) molecule comprising amino acid residues 248 – 476 of SEQ ID NO:1, said method comprising:
  - (a) determining the points of interaction between a crystalline form of the ligand binding domain of a FXR, and one or more known ligand(s) therefore utilizing structure coordinates derived from X-ray diffraction data obtained from crystals of said FXR molecule or molecular complex thereof to define said points of interaction, wherein said structure coordinates are set forth in Appendix 1, or a portion thereof sufficient to define the points of interaction between said ligand binding domain and said ligand(s); and
  - (b) analyzing said test compound to determine whether similar points of interaction exist between said test compound and said ligand binding domain.
  - 32. 37. Cancelled.